UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: September 22, 2011

SUBJECT: Picoxystrobin; Report of the Residues of Concern Knowledgebase Subcommittee (ROCKS)

PC Code: 129200
Decision No.: 432411
Petition No.: 0F7722
Risk Assessment Type: N/A
TXR No.: N/A
MRID No.: N/A

DP Barcode: D392813
Registration No.: 352-IGO
Regulatory Action: Section 3 Registration
Case No.: N/A
CAS No.: 117428-22-5
40 CFR: N/A

FROM: Elizabeth Holman, ROCKS Executive Secretary
Risk Assessment Branch 2
Health Effects Division (7509P)

THROUGH: Christine L. Olinger, ROCKS Co-Chair
Edward J. Scollon, Ph.D., ROCKS Co-Chair
Health Effects Division (7509P)

TO: Picoxsytrobin Risk Assessment Team
Risk Assessment Branch 3
Health Effects Division (7509P)

The ROCKS met on August 10, 2011 to discuss the residues of concern for the fungicide picoxystrobin in/on cereal grains, legume vegetables, soybeans, canola and associated livestock commodities in the U.S.

Team Members:
Meheret Negussie, Ibrahim Abdel-Saheb, Steve Funk, Whang Phang, Cassi Walls

ROCKS Members Attended:
Ray Kent, George Kramer, Richard Loranger, Christine Olinger, Edward Scollon, Leung Cheng, William Irwin, Elizabeth Holman, Ideliz Negron, Chester Rodriguez, Dennis McNeilly, Reuben Baris, Greg Orrick

Received in RPC 10/19/2011 EHW

Material Reviewed:

- Briefing Materials: Picoxystrobin (PC Code 129200) ROCKS Submission

Background:

Picoxystrobin is a new fungicide proposed for use on cereal grains (except rice), legume vegetables, soybeans, canola and associated livestock commodities in the U.S. Picoxystrobin inhibits mitochondrial respiration by blocking electron transfer at the Qo center of cytochrome bc1. It is registered in European, African and Latin American countries for uses on cereal grains and other commodities. In the U.S., the proposed use pattern for a 2 lb ai/gal SC formulation of picoxystrobin, involves ground or aerial equipment at a maximum single application rate of 0.2 lb ai/A/application.

Committee Decision:

Table 1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression for Picoxystrobin.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Picoxystrobin + Compounds 2, 3, and 8	Picoxystrobin
	Rotational Crop	Picoxystrobin[2]	Picoxystrobin
Livestock	Ruminant	Picoxystrobin + Compounds 2, 3, and 8	Picoxystrobin
	Poultry	Picoxystrobin + Compounds 2, 3, and 8	Picoxystrobin
Drinking Water		Picoxystrobin + Compounds 2, 3, 7, and 8	Not Applicable

[1] Please see attached Appendix 1 for parent and metabolite names and structures.
[2] Assuming a plant-back interval (PBI) of 180 days or longer.

Toxicology:

Across species and sexes, exposure to picoxystrobin results primarily in decreased body weight, liver effects (mainly hypertrophy and hyperplasia), and irritation of the mucosal membranes (e.g. GI tract leading to diarrhea, severe eye irritation). There was an increase in the incidence of testicular interstitial cell adenomas in male rats and live tumors in male mice. The carcinogenic potential of picoxystrobin will be assessed by the Cancer Assessment Review Committee. Based on rat metabolism studies, 77-82% of administered doses (AD) were absorbed, and have little potential for accumulation (>73% eliminated via urine and feces within 48 hours, >92% within 120 hours). Major route of elimination was via feces (66-72% AD) with enterohepatic circulation, and minimal differences were observed between sexes.

Quantitative structure-activity relationship (QSAR) analysis using DEREK v.12 did not indicate any potential effects specific to humans that were not otherwise evaluated in the existing animal database.

Rationale:

For plants (primary and rotational crops) and livestock commodities, the ROCKS recommends that parent picoxystrobin be the residue of concern for the tolerance expression. For risk

assessment purposes, compounds 2, 3 and 8 should be included in primary crops and livestock commodities. For drinking water, a total residue approach should be used for the risk assessment. The reasoning behind these recommendations is as follows:

Primary Crops
The registrant submitted apple (non-GLP), canola, soybean, wheat, and metabolism studies on picoxystrobin, with labels in the [^{14}C-phenyl (U)] (canola and soybean only), [^{14}C-pyridinyl], or [^{14}C-phenyl]- ring. In primary crops, parent picoxystrobin was the major residue for both radiolabels: canola foliage (70-72% TRR), canola seed (89-94%TRR), wheat forage (50-56% TRR), wheat straw (20-21% TRR), and apples (53-55%). In soybean forage and seed and wheat grain, several other major residues were observed, primarily glucose conjugates of various metabolites.

In crop field trials on field and sweet corn, wheat, barley, canola, beans, and peas, parent picoxystrobin was the predominant major residue. In addition, Compounds 2, 3, and 8 were major residues in several primary crops, including peas and corn. Toxicological data is not available for these metabolites and thus they cannot be excluded from risk assessment on the basis of toxicological impacts. Compounds 2 and 8 are similar in structure to parent picoxystrobin and therefore, not anticipated to be more toxic than the parent. Compound 3 is a cleavage product but is considered to have equivalent toxicity to parent picoxystrobin for the purpose of the ROCKS recommendation, since toxicity data are not available and there is no other information available that suggest that compound 3 does not have any toxic effects

The use of parent picoxystrobin is an adequate measure for tolerance enforcement and in primary crops for these proposed uses. For risk assessment purposes, ROCKS recommends that parent picoxystrobin and Compounds 2, 3, and 8 be included, an approach that should be conservatively protective. For dietary burden calculations, parent picoxystrobin and Compounds 2, 3, and 8 should be included assuming that these metabolites are equivalent to parent in terms of transferring to livestock tissues and milk. ROCKS also notes the lack of a metabolism study on root crops and given the significant soil metabolism of picoxystrobin, such data may be needed to support future uses on root crops.

Rotational Crops
Confined rotational crop studies were conducted on wheat (small grain), lettuce (leafy vegetable), and carrot (root vegetable) planted at 30 and 197 days after soil treatment. Field accumulation studies on spring wheat, lettuce and carrots were also submitted, with commodities grown outdoors (305 DAT) in field soil plots which had previously been planted with winter wheat. These studies indicate extensive degradation of picoxystrobin, particularly in root crops, and show the potential for substantially more exposure to various metabolites compared to parent picoxystrobin. However, comparison of the confined studies at 197 days to the field studies at 107 days indicate that the metabolite concentrations in the field studies are approximately one-tenth the value observed in confined studies. With metabolite concentrations <0.01 ppm in the more realistic field accumulation studies, the potential for exposure to these metabolites is considered to be minimal.

Therefore, under the proposed field conditions and a plant-back interval (PBI) of 180 days (for crops not on the label), one would not expect significant exposure to the parent or metabolites.

In the event of future uses with shorter PBI's, additional field studies may be needed to characterize metabolite residues, particularly compounds 11, 20, 29, and 30 (which were observed at high concentrations in the confined studies). The use of parent picoxystrobin is an adequate measure for tolerance enforcement and risk assessment purposes in rotational crops for the currently proposed uses.

Livestock

The metabolism of picoxystrobin was investigated in both laying hens and lactating goats. In a ruminant metabolism study, picoxystrobin was the major residue in fat (55-81% TRR), but only a minor residue in liver and kidney (1-4% TRR). The primary metabolite identified was Compound 2 in goat liver (6%) and compound 7 in goat kidney (15% TRR). Extensive metabolism was observed in the liver and kidney, with multiple minor metabolites (<4% TRR) observed in these matrices. The submitted goat metabolism study did not characterize or identify metabolites in milk. The picoxystrobin RA team indicated that feeding studies conducted at 400 ppm resulted in fat residues ranging from 0.005-0.08 ppm. For poultry, the radioactive residues in tissues (liver, fat, and muscle) whose values were greater than 0.01 ppm were not characterized or identified. In hen excreta, parent picoxystrobin was identified (4-8% AD); Compound 2, 3, 7, 10, 33, 34, and 48 were also identified at <10% AD. In the egg yolk, the parent was detected at (2% (0.005 ppm) &1% (0.003 ppm) and Compound 3, 7, and 10 were identified at low levels (0.001-0.005 ppm).

For these proposed uses, parent picoxystrobin is an adequate measure for tolerance enforcement purposes in livestock commodities. For risk assessment purposes, compounds 2, 3, and 8 should be included in these commodities. As noted in the discussion under "Primary Crops," parent picoxystrobin and Compounds 2, 3, and 8 should be included in the dietary burden calculations and the three metabolites assumed to be equivalent to parent in terms of transferring to livestock tissues and milk. However, for future uses resulting in a higher dietary burden, additional livestock metabolism studies may be needed to further characterize the metabolite residues in milk and poultry matrices.

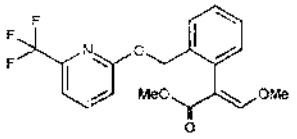
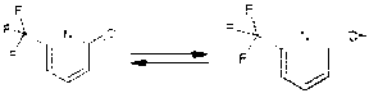
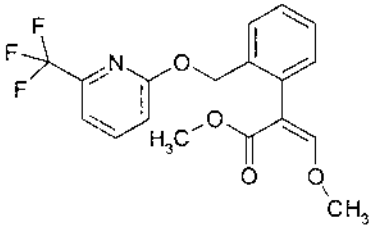
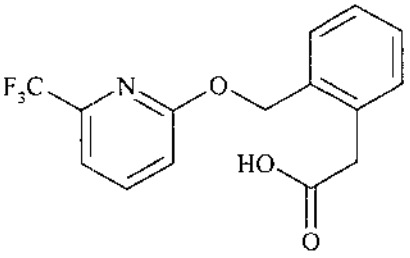
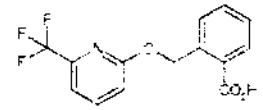
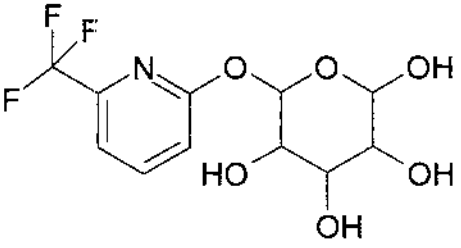
Drinking Water

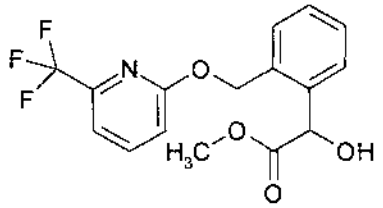
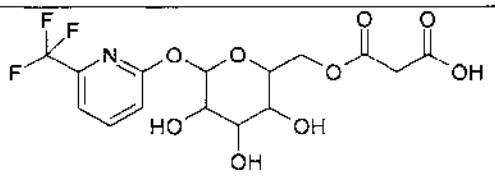
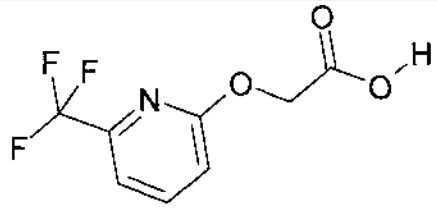
Picoxystrobin's major route of dissipation is aerobic biotransformation, with aqueous photolysis as a primary route that would only be significant in shallow clear waters. The major environmental degradates of picoxystrobin include Compound 2, Compound 3, Compound 4, Compound 7, Compound 8, and Compound 12. However, Compounds 4 and 12 were only major degradates under aqueous photolysis conditions and exposure is not anticipated except in shallow clear waters. No animal studies are available to characterize the toxicity of these metabolites. Compounds 2, 7, and 8 are all similar in structure to parent picoxystrobin and therefore not anticipated to be more toxic than the parent. Compound 3 is a cleavage product, which as previously discussed may have different toxicity than parent picoxystrobin.

For the proposed uses currently under review, a total residue approach should be used in the drinking water assessment, including parent and the following major environmental degradates: Compound 2, Compound 3, Compound 7, and Compound 8. For future uses that involve aquatic applications, inclusion of Compounds 4 and 12 may need to be considered, given the potential for these degradates to form through aqueous photolysis.

Recommended Tolerance Expression:
The ROCKS recommends the following language for the tolerance expression for plant and livestock commodities:

Tolerances are established for residues of the fungicide picoxystrobin, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only picoxystrobin, methyl (αE)-α-(methoxymethylene)-2-[[[6-(trifluoromethyl)-2-pyridinyl]oxy]methyl]benzeneacetate.

Appendix 1. Structures of Picoxystrobin Major Metabolites and Degradates		
Code Name	Chemical Abstracts Name (IUPAC Name)	Structure
Picoxystrobin	methyl *(E)*-2-{2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl}-3-methoxyacrylate	
Compound 2 IN-QDY62 (R403092)	4-(cyclopropylhydroxymethylene)-3,5-dioxocyclohexanecarboxylic acid	
Compound 3 IN-QDK50 (R403814)	6-(trifluoromethyl)pyridin-1H-2-one (6-(trifluoromethyl) pyrindin-2-ol (preferred name))	
Compound 4	methyl (Z)-2-{2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl}-3-methoxyacrylate	
Compound 7 (R408631)	2-[2-[6-trifluoromethyl) pyridin-2-yloxymethyl] phenyl] acetic acid	
Compound 8 IN-QDY63 (R408509)	2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl]benzoic acid	
Compound 11 IN-QGS45 (R409465)	6-trifluoromethyl-2-glucosylpyridine	

Appendix 1. Structures of Picoxystrobin Major Metabolites and Degradates		
Code Name	Chemical Abstracts Name (IUPAC Name)	Structure
Compound 12	methyl 2-hydroxy-{2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl}-acetate	
Compound 20 (R415833)	6-trifluoromethyl-2-(6-malonylglucosyl)pyridine	
Compound 29 (R414535) Note: Mixture of 3,4 and 6-isomers	2-{n-(3-hydroxy-3-methylglutaryl)glucosyl}-6-{trifluoromethyl)pyridine, where n is a mixture of 3, 4 and 6	Structure not available.
Compound 30 (R409665)	2-(6-(trifluoromethyl)pyridin-2-yloxyacetic acid	

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Chemical Name: Picoxystrobin

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